## REMARKS/ARGUMENTS

The September 10, 2003 Official Action and references cited therein have been carefully considered. In view of the amendments submitted herewith and the following remarks, favorable reconsideration and allowance of this application are respectfully requested.

**Status of the prosecution:**

Claims 45, 54-65, 70-78 and 80 are pending and were examined. All rejections were on the basis of prior art, as summarized below.

Claims 45, 54-58, 70 and 75 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by any one of (1) Srivastava et al. (1997, Carcinogenesis 18: 1799-1808); (2) Russo et al. (1990, J. Natl. Cancer Inst. 82: 1286-1289); or (3) Russo et al. (1990, Br. J. Cancer 62: 2343-2347).

Claims 45, 54, 58, 60-64, 70 and 72 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Grattarola (1976, J. Natl. Cancer Inst. 56: 11-16).

Claims 45, 70-72 and 77 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Saal et al. (1991, Fertil. Steril. 56: 225-229) as evidenced by Russo et al. (1990, Br. J. Cancer 62: 2343-2347).

Claims 45 and 70-77 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Anapliotou et al. (1996, Fertil. Steril. 66: 305-311) as evidenced by Russo et al. (1990, Br. J. Cancer 62: 2343-2347).

Claim 59 was rejected under 35 U.S.C. §103(a) as allegedly obvious over any one of (1) Srivastava et al. (1997, Carcinogenesis 18: 1799-1808); (2) Russo et al. (1990, J. Natl. Cancer Inst. 82: 1286-1289); or (3) Russo et al. (1990, Br. J. Cancer 62: 2343-2347), in view of Silverstein et al. (1994, Cancer 73: 1673-1677, abstract only).

Claim 65 was rejected under 35 U.S.C. §103(a) as allegedly obvious over any one of (1) Srivastava et al. (1997, Carcinogenesis 18: 1799-1808); (2) Russo et al. (1990, J. Natl. Cancer Inst. 82: 1286-1289); or (3) Russo et al. (1990, Br. J. Cancer 62: 2343-2347), in view of Mgbonyebi et al. (1997, Proc. Ann. Meeting Am. Soc. Cancer Res. pp A1977 XP002109660).

Claim 78 was rejected under 35 U.S.C. §103(a) as allegedly obvious over any one of (1) Srivastava et al. (1997, Carcinogenesis 18: 1799-1808); (2) Russo et al. (1990, J. Natl. Cancer Inst. 82: 1286-1289); or (3) Russo et al. (1990, Br. J. Cancer 62: 2343-2347), in view of any one of (1) Platanias et al. (1998, J. Biol. Chem. 273: 5577-5581); (2) Oberg et al. (1989, J. Natl. Cancer Inst. 81: 531-535); (3) Recchia et al. (1998, Clin. Ter. 149: 203-208) or (4) Robinson et al. (1990, Breast Cancer Res. Treat. 15: 95-101.

Claim 80 was rejected under 35 U.S.C. §103(a) as allegedly obvious over any one of (1) Srivastava et al. (1997, Carcinogenesis 18: 1799-1808); (2) Russo et al. (1990, J. Natl. Cancer Inst. 82: 1286-1289); or (3) Russo et al. (1990, Br. J. Cancer 62: 2343-2347), in view of the Sigma Chemical Co. catalog (1995, page 263).

Claims 45, 55, 56 and 60 are amended and claim 54 is canceled herein. Claim 45 has been amended to include the limitation of claim 54. Claims 55, 56 and 60 have been amended for proper dependency and consistency of language in view of the amendment to claim 45. No new matter has been added. Applicants respectfully assert that the presently amended claims are in condition for allowance, for the reasons set forth below.

**The claims as amended are drawn to novel subject matter:**

Claims 45, 54-58, 70 and 75 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by any one of (1) Srivastava et al. (1997, Carcinogenesis 18: 1799-1808); (2) Russo et al. (1990, J. Natl. Cancer Inst. 82: 1286-1289) (hereinafter Russo et al. 1990(1)); or (3) Russo et al. (1990, Br. J. Cancer 62: 2343-2347) (hereinafter Russo et al. 1990(2)). According to the examiner, each of Srivastava, Russo et al. 1990(1) and Russo et al. 1990(2) teach "a method of treating/preventing DMBA-induced mammary tumor (non invasive, invasive, carcinoma) by administering 100 IU hCG." The examiner asserts therefore that claim 45 and claims 54-58, 70 and 75, dependent therefrom, are anticipated by the three aforementioned references. Applicants traverse this rejection as applied to the presently amended claims.

None of the cited references discloses a method of treating or preventing clinically manifest mammary tumors by administering hCG to a host having a clinically manifest mammary tumor. Indeed, each of the three cited references discloses a similar experimental

protocol (set forth in Fig. 1 of Srivastava et al.; in Fig. 1 of Russo et al. 1990(1) and at 2344 (Materials & Methods) of Russo et al. 1990(2). The protocol calls for: (a) injecting 45 or 50 day-old virgin Sprague-Dawley rats with DMBA (or saline); and (b) 20 or 21 days later, injecting the rats with hCG (or saline) periodically for an ensuing number of days. Thus, in each protocol, only 20 or 21 days elapsed between treatment with the carcinogen and administration of the first dose of hCG. In no instance do any of the three references disclose that tumors were clinically manifest in the rats at the initiation of hCG treatment. On the contrary, Russo et al. 1990(2) (page 2344, right col., last paragraph and Fig. 1) specifically disclose that animals did not begin developing palpable tumors until six weeks after DMBA injection. Likewise, Russo et al. 1990(1) (Table 1) report a latency period for tumor development in the DMBA + hCG (21 days later) (Group IV) of 49-154 days. From these data it is clear that palpable tumors were not present at 21 days post-DMBA treatment, when hCG was administered. Similarly, Srivastava et al. report that the earliest finding of a mammary tumor following DMBA administration was at 70 days of age (one animal out of 32 had a tumor). Thus Srivastava et al. also teach that the animals did not possess clinically manifest tumors at the time hCG treatment was initiated at 65 days of age.

Since none of the cited references discloses hCG treatment of hosts having clinically manifest tumors, and each indeed specifically discloses that clinically manifest tumors were not present at the time hCG treatment was initiated, none of the cited references can be said to disclose the invention as presently claimed in claim 45. Accordingly, the rejection of claims 45, 55-58, 70 and 75 under 35 U.S.C. §102(b) on the basis of those references is untenable and should be withdrawn.

Claims 45, 54, 58, 60-64, 70 and 72 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Grattarola (1976, J. Natl. Cancer Inst. 56: 11-16). According to the examiner, the method taught by Grattarola, i.e., "administering 15,000 IU hCG to advanced breast cancer patients who are either pre-menopausal and post-menopausal, and had undergone surgery," would inherently result in the purpose stated in the preamble of the instant claims, thereby anticipating those claims. Applicants traverse this rejection as applied to the presently amended claims.

Grattarola nowhere discloses a method of treating or preventing clinically manifest mammary tumors by administering hCG to a host having a clinically manifest mammary

tumor. In actuality, the only hCG "treatment" mentioned by Grattarola at all was not even a treatment for mammary tumors – it was instead a means of confirming that the increased testosterone excretion observed in some women following ovariectomy (as an adjunct to mastectomy) was due to gonadotropins (see, e.g., page 11, right col., second full paragraph; left column, second full paragraph *et seq.*). In fact, the only hCG administration reported by Grattarola was to post-mastectomy, post-ovariectomy patients (see, e.g., page 12, left col.), who, by definition, could not have had a clinically manifest mammary tumor at the time, because those tumors had been removed previously by surgery. Moreover, it should be noted that Grattarola nowhere teaches or discloses the use of hCG to treat mammary tumors, whether clinically manifest or not. Grattarola discloses a preferred treatment for breast cancer that comprises ovariectomy (as an adjunct to mastectomy), combined with corticosteroids (see, e.g., page 15, right col., first full paragraph).

Because Grattarola does not disclose hCG treatment of hosts having clinically manifest tumors, and indeed does not disclose administration of hCG to treat mammary tumors at all, Grattarola cannot be said to disclose the invention as presently claimed in claim 45. Accordingly, the rejection of claims 45, 58, 60-64, 70 and 72 under 35 U.S.C. §102(b) on the basis of Grattarola is untenable, and should be withdrawn.

Claims 45, 70-72 and 77 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Saal et al. (1991, Fertil. Steril. 56: 225-229) as evidenced by Russo et al. 1990(2). Claim 54 was not rejected on this ground. Inasmuch as the limitation of claim 54 now appears in claim 45, applicants assert that the invention of claim 45 and all claims dependent therefrom is novel in view of Saal et al. as evidenced by Russo et al. (1990). Withdrawal of the rejection is therefore requested.

Claims 45 and 70-77 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Anapliotou et al. (1996, Fertil. Steril. 66: 305-311) as evidenced by Russo et al. 1990(2). Claim 54 was not rejected on this ground. Inasmuch as the limitation of claim 54 now appears in claim 45, applicants assert that the invention of claim 45 and all claims dependent therefrom is novel in view of Anapliotou et al. as evidenced by Russo et al. (1990). Withdrawal of the rejection is therefore requested.

**The claims as amended are drawn to non-obvious subject matter:**

Claim 59 was rejected under 35 U.S.C. §103(a) as allegedly obvious over any one of (1) Srivastava et al. (1997, Carcinogenesis 18: 1799-1808); (2) Russo et al. 1990(1) or (3) Russo et al. 1990(2) in view of Silverstein et al. (1994, Cancer 73: 1673-1677, abstract only). The examiner asserts that any one of the primary references teaches that "hCG has a protective effect against breast cancer," and Silverstein et al. teach that tubular or lobular invasive breast mammary carcinoma is also breast cancer. The examiner asserts that it would therefore have been obvious to one of skill in the art to select patients having the specifically recited stage of breast cancer and administer hCG. Applicants traverse this rejection as applied to the presently amended claims.

In order for a *prima facie* case of obviousness to be established under 35 U.S.C. §103, there must be a motivation in the art to combine the references identified by the examiner. The prior art must suggest the desirability of the claimed invention. The mere fact the references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. (MPEP 2143.01).

Claim 59 depends from claim 45, which is amended to recite that hCG is administered to a host having a clinically manifest mammary tumor. As explained above, none of the primary references teaches or suggests the use of hCG to treat patients having clinically manifest mammary tumors. Silverstein et al., in teaching that tubular or lobular invasive breast mammary carcinoma is also breast cancer, does not supply the teaching that is clearly absent from the primary references, that is, to use hCG to treat patients having clinically manifest mammary tumors. Thus, since there is no suggestion in the cited references, alone or combined, to modify their teachings to arrive at the invention as presently claimed in claim 59, the cited references fail to establish a *prima facie* case of obviousness of the claimed invention. Withdrawal of the rejection is therefore requested.

Claim 65 was rejected under 35 U.S.C. §103(a) as allegedly obvious over any one of (1) Srivastava et al. (1997, Carcinogenesis 18: 1799-1808); (2) Russo et al. 1990(1); or (3) Russo et al. 1990(2), in view of Mgbonyebi et al. (1997, Proc. Ann. Meeting Am. Soc. Cancer Res. pp A1977 XP002109660). The examiner again asserts that any one of the primary references teaches that hCG has a protective effect against breast cancer, and Mgbonyebi et al. teach that hCG is effective in inhibition of estrogen positive breast cancer

cells. The examiner asserts that it would therefore have been obvious to one of skill in the art to detect which breast cancer is estrogen positive and to practice the claimed invention with a reasonable expectation of success. Applicants traverse this rejection as applied to the presently amended claims.

Claim 65 depends from claim 45, which is amended to recite that hCG is administered to a host having a clinically manifest mammary tumor. As explained above, none of the primary references teaches or suggests the use of hCG to treat patients having clinically manifest mammary tumors. Mgbonyebi et al., in teaching that that hCG inhibits growth of estrogen-positive breast cancer cells, does not supply the teaching that is clearly absent from the primary references, that is, to use hCG to treat patients having clinically manifest mammary tumors. Again then, there is no suggestion in the cited references, alone or combined, to modify their teachings to arrive at the invention as presently claimed in claim 65. Since the references fail to supply the motivation to make the invention as claimed, clearly the references also supply no expectation of success in practicing the claimed invention. Accordingly, the cited references fail to establish a *prima facie* case of obviousness of the invention of claim 65, and withdrawal of the rejection is therefore requested.

Claim 78 was rejected under 35 U.S.C. §103(a) as allegedly obvious over any one of (1) Srivastava et al. (1997, Carcinogenesis 18: 1799-1808); (2) Russo et al. 1990(1); or (3) Russo et al. 1990(2) in view of any one of (1) Platanias et al. (1998, J. Biol. Chem. 273: 5577-5581); (2) Oberg et al. (1989, J. Natl. Cancer Inst. 81: 531-535); (3) Recchia et al. (1998, Clin. Ter. 149: 203-208) or (4) Robinson et al. (1990, Breast Cancer Res. Treat. 15: 95-101. The primary references were applied as in the other rejections, while the four secondary references were cited for their teaching that Type 1 interferon has anti-tumor activity. According to the examiner, it would have been obvious in view of the cited references to administer Type 1 interferon together with hCG, which is the examiner's view of the subject matter of claim 78.

Applicants traverse this rejection as applied to the claims as presently amended. In view of the amendment to claim 45, dependent claim 78 recites a method comprising administering hCG and Type 1 interferon to a host having a clinically manifest mammary tumor. As stated above, the primary references fail to disclose, teach or suggest the use of

hCG for the treatment of clinically manifest mammary tumors. The secondary references' teachings of the anti-tumor function of Type 1 interferon do nothing to supply the teaching that is clearly absent from the primary references, that is, to use hCG to treat patients having clinically manifest mammary tumors. Again then, there is no suggestion in the cited references, alone or combined, to modify their teachings to arrive at the invention as presently claimed in claim 78. Since the references fail to supply the motivation even to make the invention as claimed, clearly the references also supply no expectation of success in practicing the claimed invention. Accordingly, the cited references fail to establish a *prima facie* case of obviousness of the invention of claim 78, and withdrawal of the rejection is therefore requested.

Claim 80 was rejected under 35 U.S.C. §103(a) as allegedly obvious over any one of (1) Srivastava et al. (1997, Carcinogenesis 18: 1799-1808); (2) Russo et al. 1990(1); or (3) Russo et al. 1990(2), in view of the Sigma Chemical Co. catalog (1995, page 263). The primary references again were applied as in the other rejections, while the Sigma catalog was cited for teaching the existence of recombinant hCG According to the examiner, it would have been obvious in view of the cited references to administer r-hCG to treat or prevent mammary tumors.

Applicants again traverse this rejection as applied to the claims as presently amended. In view of the amendment to claim 45, dependent claim 80 recites a method comprising administering r-hCG to a host having a clinically manifest mammary tumor. As stated above, the primary references fail to disclose, teach or suggest the use of hCG for the treatment of clinically manifest mammary tumors. The secondary reference's teaching of r-hCG does nothing to supply the teaching that is absent from the primary references, that is, to use hCG to treat patients having clinically manifest mammary tumors. Again then, there is no suggestion in the cited references, alone or combined, to modify their teachings to arrive at the invention as presently claimed in claim 80. Since the references fail to supply the motivation even to make the invention as claimed, clearly the references also supply no expectation of success in practicing the claimed invention. Accordingly, the cited references fail to establish a *prima facie* case of obviousness of the invention of claim 80, and withdrawal of the rejection is therefore requested.

**Conclusion:**

In view of the amendments submitted herewith and the foregoing remarks, the presently pending claims are believed to be in condition for allowance. Applicants respectfully request early and favorable reconsideration and withdrawal of the rejections set forth in the September 10, 2003 Official Action, and allowance of this application.

Respectfully submitted,

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